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(54) Title: PRODRUG ESTERS OF PHENOLIC 2-PIPERIDINO-1-ALKANOLS

(57) Abstract

Phenolic prodrug esters of certain 1-(hydroxyphenyl)-2-piperidino-1-alkanol derivatives, which are useful in the treatment of stroke, traumatic head injury and CNS degenerative disease; and intermediates useful in their synthesis.

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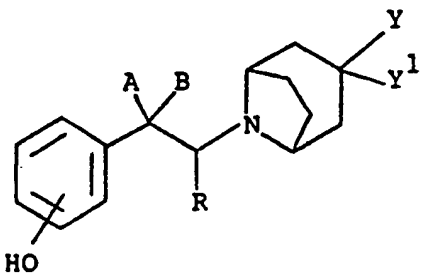
PRODRUG ESTERS OF PHENOLIC 2-PIPERIDINO-1-ALKANOLS

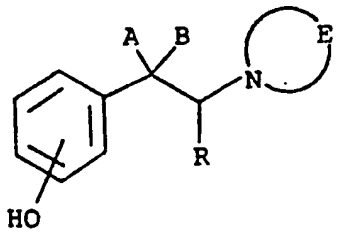
The present invention is directed to prodrug esters of phenolic 2-piperidino-1-alkanols, as depicted by the formulas (I) and (II), below; to pharmaceutical compositions thereof; to a method of treating stroke, traumatic head injury, or a CNS degenerative disease therewith; and to ketone intermediates of the formulas (III) and (IV), below, which are useful in their synthesis.

The phenolic compounds from which the present compounds derive are disclosed in my International Applications Published Under the Patent Cooperation Treaty, International Publication Nos. WO 90/14087 and WO/14088, both published on November 29, 1990, and hereby incorporated by reference. These phenolic compounds are of the formulas



---(A)

and

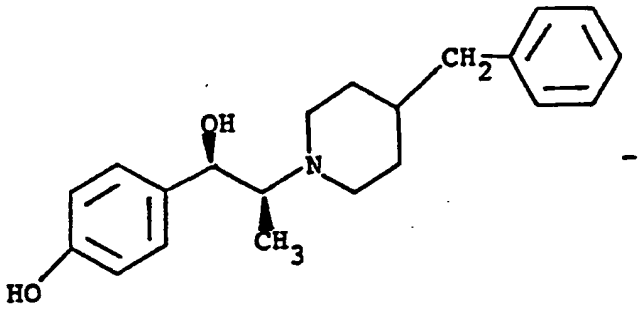


---(B)

wherein A and B are taken separately and A is hydrogen and B is hydroxy, or A and B are taken together and are oxygen (forming a carbonyl group); and the groups R, E, Y and Y^1 are as defined below for the corresponding ester derivatives of the formulas (I), (II), (III) and (IV).

The compounds of the formulas (A) and (B) wherein the groups A and B are taken separately to form a 1-alkanol, like the present compounds of the formulas (I) and (II), generally possess selective antiischemic and excitatory amino acid receptor blocking activity (i.e., a neuroprotective effect) in good measure, while at the same time they have lowered or no significant hypotensive effect.

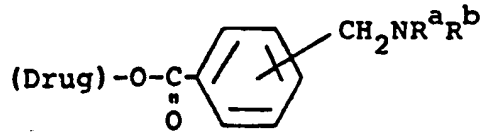
Ifenprodil, a racemic, so-called dl-erythro compound having the relative stereochemical formula



---(C)

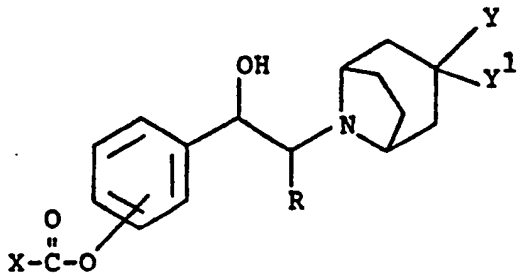
has been shown to possess antiischemic and excitory aminoacid receptor blocking activity; Gotti et al., J. Pharm. Exp. Therap., v. 247, pp. 1211-21 (1988); Carter et al., loc. cit., pp. 1222-32 (1988). See also French Patent 2546166. However, in ifenprodil, this activity is not selective. Indeed ifenprodil is marketed as a hypotensive agent, a utility shared by a number of close analogs; Carron et al., U.S. Patent 3,509,164; Carron et al., Drug Res., v. 21, pp. 1992-1999 (1971).

So-called prodrug esters, which in general enhance oral absorption and are hydrolyzed in vivo to form the active component of the ester, have become quite common in the medicinal art. For example, Bundgaard et al., J. Med. Chem., v. 32, pp. 2503-7 (1989) have described certain prodrug esters of the type



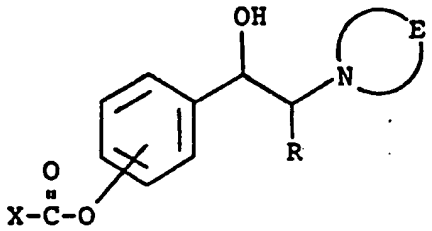
wherein R^a and R^b are taken separately, R^a is hydrogen or lower alkyl, and R^b is lower alkyl; or R^a and R^b are taken together with the nitrogen to which they are attached to form, for example, a morpholine or 4-methylpiperazine ring.

The present invention is directed to so-called pro-drug esters of the formulas



---(I)

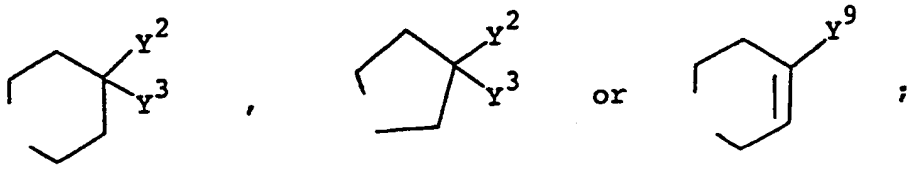
and



---(II)

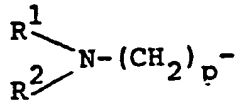
wherein

E is



R is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

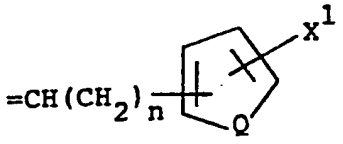
X is phenyl, benzyl, (C_1-C_3)alkoxy, phenoxy or one of said groups substituted on aromatic carbon by



p is 1 or 2;

R^1 and R^2 are taken separately and are each independently hydrogen or (C_1-C_6)alkyl, or R^1 and R^2 are taken together with the nitrogen to which they are attached to form a pyrrolidine, piperidine or morpholine ring, or one of said rings substituted by (C_1-C_3)alkyl;

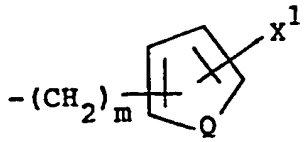
when either Y and Y^1 or Y^2 and Y^3 are taken together, they are



; or

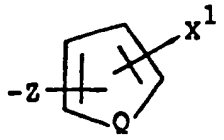
when Y and Y^1 are taken separately,

Y is hydrogen or OH, and Y^1 is



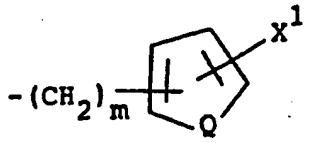
; or

Y is hydrogen and Y^1 is



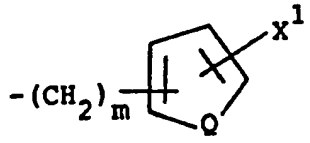
;

when Y^2 and Y^3 are taken separately, and Y^2 is OH and Y^3 is



;

Y^9 is



;

n is 0, 1, 2 or 3;

m is 0, 1, 2, 3 or 4;

Q is S or CH=CH;

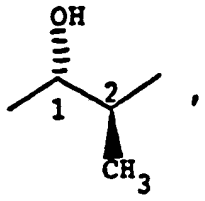
X^1 is hydrogen, (C_1-C_3)alkyl, (C_1-C_3)alkoxy or halo; and

Z is O, S, SO or SO_2; or

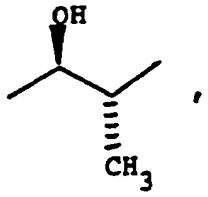
a pharmaceutically-acceptable acid addition salt thereof.

Said acid addition salts include, but are not limited to, those formed with such acids as HCl, H_2SO_4, H_3PO_4, HNO_3, CH_3SO_3H, $pCH_3C_6H_4SO_3H$, acetic acid, maleic acid and citric acid.

The pr ferred compounds are racemic or optically active compounds wherein R is methyl and have 1S*,2S* relative stereochemistry:



alternatively and equivalently depicted as:

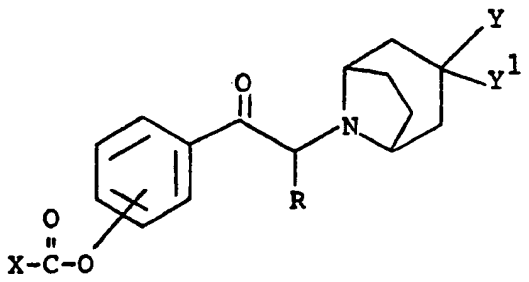


and referred to as 1R*,2R* relative stereochemistry. See Rigaudy et al., eds., IUPAC Nomenclature of Organic Chemistry, 1979 Edition, Pergamon Press, New York, 1979, p. 482. Preferred values of X are phenyl, p-(dimethylaminomethyl)phenyl, p-(diethylaminomethyl)-phenyl, m-(diethylaminomethyl)phenyl, p-(piperidino-methyl)phenyl, p-(2-methylpiperidinomethyl)phenyl and p-(morpholinomethyl)phenyl. The preferred position of the XCOO group on the benzene ring is para to the 1-hydroxyalkyl substituent.

The present invention is further directed to pharmaceutical compositions comprising a neuroprotective amount of a compound of formula (I) or (II) and to a method of treating stroke, traumatic head injury or a CNS degenerative disease in man which comprises treatment with a neuroprotective amount of one of said compounds. Said compositions and treatment method include not only the oral route of administration, wher absorption from

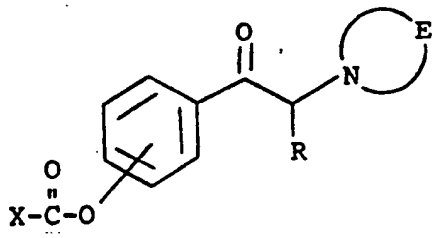
the intestinal tract is generally enhanced, but also parenteral routes of administration (e.g., intravenous, intramuscular). The present, intact prodrug esters also generally cross the blood-brain barrier, and further, are capable of hydrolysis in brain tissue once across that barrier. Thus parenteral (as well as oral) administration of these esters can lead to desirable enhancement of active drug levels in the brain.

The present invention is also directed to ketone precursors of the present 1-alkanol derivatives, of the formulas



---(III)

and



---(IV)

wherein

E, R, X, Y and Y^1 are as defined above.

It will be noted that those compounds of the formulas (I) and (II), which are 1-alkanols, possess an asymmetric C-1 carbon, while those wherein R is other than hydrogen possess a second asymmetric center at the C-2 carbon of the alkanol. Similarly, in those compounds of the formulas (III) and (IV) which are 1-alkanones

wherein R is other than hydrogen possess a C-2 asymmetric carbon. It will be evident to those skilled in the art of organic chemistry, therefore, that such compounds can be resolved into optical isomers showing equal but opposite rotation of plane polarized light. For example, all of these compounds are potentially resolved by fractional crystallization of their diastereomeric acid addition salts formed with an optically active acid; while the alcohols are also potentially resolved by chromatography or fractional crystallization of esters derived by reaction with activated forms of optically active acids or with optically active isocyanates. Thus, the present invention should not be construed as limited to the racemic forms of the present compounds.

The present invention is readily carried out. According to the preferred route, the compounds of the above formula (I) and (II) are formed by conventional hydride reduction of a corresponding, already acylated ketone of the above formula (III) or (IV). Hydride reducing agents generally useful in this reduction include lithium aluminum hydride and sodium borohydride. Generally an excess of the hydride reducing agent is employed, but to avoid reduction of the ester group, lithium aluminum hydride is employed at low temperature, e.g., at -50°C to -100°C, conveniently about -78°C, the temperature of a dry ice-acetone bath. In any event, the hydride reduction is carried out in a reaction-inert solvent, such as tetrahydrofuran in the case of lithium aluminum hydride and absolute ethanol in the case of sodium borohydride. With sodium borohydride temperature is less critical, with temperatures in the range of 0-30°C being generally preferred.

As used in the preceding paragraph, and elsewhere herein, the expression "reaction inert solvent" refers to any solvent which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Further according to the preferred method of preparing the present compounds of the above formulas (I) and (II), the acylated ketone precursors of the above formulas (III) and (IV) are obtained by acylation of a known ketone derivative, respectively, of the formulas (A) and (B), above, wherein A and B are taken together to form a carbonyl group. Said acylation is readily accomplished by a number of conventional methods which are well known in the organic chemical art. When the ketone (A) or (B) contains a tertiary aliphatic alcohol group (which is the case when either Y or Y^2 is hydroxy), this acylation is necessarily selective, but still, in general, is readily accomplished because of the greater activity of the phenolic group relative to the hindered tertiary, alcoholic group. The preferred methods borrow from coupling methods used in the synthesis of peptides. According to one of the preferred methods, a substantially molar equivalent of the acid is coupled with the phenolic ketone by the action of substantially one molar equivalent of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide. This coupling is generally carried out in a reaction-inert solvent such as methylene chloride in the presence of 10-20% molar excess of a tertiary amine such as 4-dimethylaminopyridine. Temperature is not critical, with temperatures in the range of 0-50°C being generally satisfactory, and ambient temperatures (generally about 17-27°C) preferred, since the cost of heating or cooling is avoided.

Alternatively, the compounds of the formulas (I) and (II) are obtained directly by acylation of the appropriate, known phenolic 1-alkanol compound of the above formulas (A) and (B) wherein A and B are taken separately, A is hydrogen and B is hydroxy. Indeed, when the 1-alkanol is already available in resolved form, this is a preferred route to the optically active forms of the present esters.

The ketonic and 1-alkanol precursors of the formulas (A) and (B) depicted above are disclosed in my Published International Patent Application Number WO 90/14087 cited above. In the ketones of that reference wherein the phenol group is protected, the protecting group is removed by the same methods there particularly disclosed for the deprotection of phenol-protected 1-alkanol derivatives. Such a deprotection method is also specifically described in Preparations detailed below.

The inherent antiischemic activity and ability of the present prodrug esters to block excitatory amino acid receptors is reflected from the study of the corresponding phenolic 1-alkanol compounds (of the above formulas (A) and (B) wherein A and B are taken separately, A is hydrogen and B is hydroxy). These biological methods are detailed in the prior art references cited above, viz., Gotti et al., Carter et al. and my published International application WO 90/14088.

The present prodrug esters are dosed at weight levels which are chemically equivalent to the weight levels of the fully active phenolic forms, as detailed in my published International application WO 90/14088 cited above. For example, for a 10 mg dose of a phenol

having a molecular weight of 327, the amount of a prodrug ester having a molecular weight of 516 will be

$$10 \text{ mg} \times \frac{516}{327} = 15.8 \text{ mg}$$

The present prodrug esters are formulated into oral and parenteral dosage forms according to the same conventional methods which are used in the formulation of the corresponding phenols as described in my published International application WO 90/14088.

The present invention is illustrated by the following examples, but is not limited to the details thereof.

All non-aqueous reactions were run under nitrogen for convenience and generally to maximize yields. All solvents/diluents were dried according to standard published procedures or purchased in a predried form. All reactions were stirred either magnetically or mechanically. NMR specta are recorded at 300 MHz and are reported in ppm. The NMR solvent was $CDCl_3$ unless other specified.

EXAMPLE 1

2-(4-Hydroxy-4-phenylpiperidino)-1-(4-(4-(morpholinomethyl)benzoyloxy)phenyl)-1-propanone

To a mixture of 4-(morpholinomethyl)benzoic acid (3.17 g, 12.3 mmol), 1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanone (4.0 g, 12.29 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (2.36 g, 12.31 mmol) in methylene chloride (75 mL) was added 4-dimethylaminopyridine (1.88 g, 15.39 mmol). The heterogeneous mixture was allowed to stir overnight under a nitrogen atmosphere at ambient temperature. The mixture was washed with saturated aqueous bicarbonate (2 x 50 mL), dried by filtration through phase separating filter paper, and concentrated to a glassy yellow solid. Trituration with ether and hexane yielded 5.17 g, 80% of a light yellow solid product which was suitable for further reaction without additional purification. A sample recrystallized from ethyl acetate/hexane had: m.p. 126-126.5°C; NMR ($CDCl_3$) 8.22 (d, J=8.6 Hz, 2H), 8.13 (d, J=7.8 Hz, 2H), 7.47 (t, J=7.3 Hz, 4H), 7.34-7.19 (m, 5H), 4.13 (q, J=6.6 Hz, 1H), 3.70 (t, J=4.4 Hz, 4H), 3.57 (s, 2H), 2.97-2.79 (m, 2H), 2.67-2.60 (m, 2H), 2.44 (t, J=4.5 Hz, 4H), 2.18-1.98 (m, 2H), 1.78-1.67 (m, 3H), 1.31 (d, J=6.6 Hz, 3H). IR (KBr) 3270, 2960, 2942, 2912, 2830, 2821, 1743, 1682, 1596, 1390, 1273, 1199.

Analysis calculated for $C_{32}H_{36}N_2O_5$:

C, 72.70; H, 6.86; N, 5.30.

Found: C, 72.42; H, 6.65; N, 5.25.

In like manner, other phenol-ketones of the Preparation below are converted to:

2-(4-Benzyl-4-hydroxypiperidino)-1-(4-(4-morpholinomethyl)benzoyloxy)phenyl)-1-propanone; and

2-(4-(4-Chlorophenyl)-4-hydroxypiperidino)-1-(4-(morpholinomethyl)benzoyloxy)phenyl-1-propanone.

EXAMPLE 2

Racemic (1S*,2S*)- and (1R*,2S*)-2-(4-Hydroxy-4-phenylpiperidino)-1-(4-(4-(morpholinomethyl)benzoyloxy)phenyl)-1-propanol

Sodium borohydride (0.39 g, 10.3 mmol) was partially dissolved in absolute ethanol (25 mL) and chilled to 0°C and an ice cold ethanol solution (50 mL) of the title ketone product of the preceding Example (5.0 g, 9.46 mmol) was added over 2 minutes. The reaction was stirred at 0°C overnight, and then it was quenched with glacial acetic acid (6 mL). The volatiles were distilled from the reaction mixture under vacuum while maintaining the pot temperature at or below 0°C. The residual material was flash chromatographed on silica gel (2 x 6 inches, ethyl acetate/hexane gradient elution). No product was obtained. Continued elution with a methanol/ethyl acetate gradient gave 2.90 g of the (S*,S*)-title product, which was recrystallized from ethanol to give 1.8 g of purified (S*,S*)-title product: m.p. 172-173°C; NMR ($CDCl_3$) 8.17 (d, J=8.3 Hz, 2H), 7.56-7.25 (m, 9H), 7.20 (d, J=8.5 Hz, 2H), 4.33 (d, J=9.7 Hz, 1H), 3.73 (t, J=4.6 Hz, 4H), 3.59 (s, 2H), 3.11 (dt, J=1.7, 11.6 Hz, 1H), 2.76-2.59 (m, 4H), 2.47 (t, J=4.5 Hz, 4H), 2.31-2.07 (m, 3H), 1.85 (br d, J=13.2 Hz, 3H), 0.89 (d, J=6.7 Hz, 3H); IR (KBr) 3452, 3245, 2970, 2930, 2893, 1730, 1273, 1262, 1194, 1114, 1075, 797, 758.

Analysis calculated for $C_{32}H_{38}N_2O_5$:

C, 72.43; H, 7.22; N, 5.28.

Found: C, 72.58; H, 6.95; N, 5.26.

Continued gradient elution with methanol/ethyl acetate gave 1.71 g of the (R*,S*)-title product as its acetate salt. It was further purified by recrystallization from ethanol/ether to give purified (R*,S*)-title product, 0.60 g of white powder: m.p. 164-165°C; NMR (DMSO-d_6) 8.10 (d, J=8.2 Hz, 2H), 7.54 (d, J=8.2 Hz, 2H), 7.45 (t, J=7.4 Hz, 4H), 7.31 (t, J=7.5 Hz, 2H), 7.21 (d, J=8.3 Hz, 3H), 5.82 (br s, 4H), 4.91 (d, J=4.1 Hz, 1H), 3.59 (t, J=4.6 Hz, 4H), 3.01-2.71 (m, 6H), 2.50 (m, 4H), 2.20-1.80 (m with s at 1.90 ppm, 5H), 1.64-1.60 (m, 2H), 1.01 (d, J=6.6 Hz, 3H). IR (KBr) 2961, 2856, 2820, 1733, 1268, 1201, 1071.

Analysis calculated for $C_{32}H_{38}N_2O_5 \cdot C_2H_4O_2$:

C, 69.13; H, 7.17; N, 4.74.

Found: C, 70.39; H, 6.85; N, 4.86.

By the same method, the additional products of the preceding Example are converted to:

(1S*,2S*)- and (1R*,2S*)-2-(4-Benzyl-4-hydroxypiperidino)-1-(4-(4-(morpholinomethyl)benzoyloxy)-phenyl-1-propanol; and

(1S*,2S*)- and (1R*,2S*)-2-(4-(4-Chlorophenyl)-4-hydroxypiperidino)-1-(4-(4-(morpholinomethyl)benzoyloxy)phenyl-1-propanol.

EXAMPLE 3

1-(4-(4-Diethylaminomethyl)benzoyloxy)phenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanone

The coupling of 4-diethylaminomethylbenzoic acid with 1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanone was carried out essentially as in Example 1. The crude product was treated with ether and hexane with stirring and yielded the creamy white product in 73% yield in a state of purity suitable for the reduction step. A sample recrystallized from

ether/hexane gave a white powder which had: m.p. 106-107°C; NMR ($CDCl_3$) 8.25 (d, J=8.8 Hz, 2H), 8.15 (d, J=8.3 Hz, 2H), 7.51 (t, J=7.2 Hz, 4H), 7.38-7.22 (m, 5H), 4.16 (q, J=6.7 Hz, 1H), 3.66 (s, 2H), 2.96-2.81 (m, 2H), 2.71-2.67 (m, 2H), 2.55 (q, J=7.1 Hz, 4H), 2.22-2.00 (m, 3H), 1.82-1.69 (m, 2H), 1.35 (d, J=6.7 Hz, 3H), 1.07 (t, J=7.1 Hz, 6H). IR (KBr) 3452, 2969, 2935, 2833, 1738, 1681, 1264, 1198, 1164, 1064.

Analysis calculated for $C_{32}H_{38}N_2O_4$

C, 74.68; H, 7.44; N, 5.44.

Found: C, 74.34; H, 7.28; N, 5.49.

In like manner, other phenol-ketones of the Preparation below are converted to:

1-(4-(4-(Diethylaminomethyl)benzoyloxy)phenyl)-2-(3-(phenylthio)-8-azabicyclo[3.2.1]oct-8-yl)-1-propanone;

2-(3-(4-Chlorophenylthio)-8-azabicyclo[3.2.1]oct-8-yl)-1-(4-(4-diethylaminomethyl)benzoyloxy)phenyl)-1-propanone;

1-(4-(4-(Diethylaminomethyl)benzoyloxy)phenyl)-2-(3-(2-thienylthio)-8-azabicyclo[3.2.1]oct-8-yl)-1-propanone;

2-(3-Benzyl-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl)-1-(4-(4-diethylaminoethyl)benzoyloxy)phenyl)-1-propanone; and

2-(3-Hydroxy-3-phenyl-8-azabicyclo[3.2.1]oct-8-yl)-1-(4-(4-diethylaminoethyl)benzoyloxy)phenyl)-1-propanone.

EXAMPLE 4

Racemic (1S*,2S*)- and (1R*,2S*)-1-(4-Diethylaminomethyl)benzoyloxy)phenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol

The title product from the preceding Example was reduced with sodium borohydride as in Example 2. Purification by silica gel chromatography and

recrystallization gave first (1S*,1S*)-title product (0.28 g, 28%) which had: m.p. 174-175°C (ethanol); NMR ($CDCl_3$) 8.14 (d, J=8.2 Hz, 2H), 7.50 (t, J=8.3 Hz, 4H), 7.43-7.35 (m, 4H), 7.27 (t, J=7.2 Hz, 1H), 7.18 (d, J=8.5 Hz, 2H), 4.31 (d, J=9.7 Hz, 1H), 3.64 (s, 2H), 3.08 (t, J=10.6 Hz, 1H), 2.72-2.60 (m, 4H), 2.53 (q, J=7.1 Hz, 4H), 2.27-2.05 (m, 2H), 1.92 (br s, 1H), 1.82 (br d, J=13.2 Hz, 2H), 1.05 (t, J=7.1 Hz, 6H), 0.87 (d, J=6.6 Hz, 3H); IR (KBr) 3399, 2973, 2947, 1727, 1610, 1271, 1258, 1202, 1078.

Analysis calculated for $C_{32}H_{40}N_2O$:

C, 74.39; H, 7.80; N, 5.42.

Found: C, 74.31; H, 7.76; N, 5.38.

The second product isolated was the (1R*,1S*)-title product, as its acetate salt (0.119 g, 11%) which had: m.p. 148-150°C (ethanol); NMR ($CDCl_3$) 8.14 (d, J=8.3 Hz, 2H), 7.52-7.27 (m, 10H), 7.18 (d, J=8.6 Hz, 2H), 5.45 (d, J=2.4 Hz, 1H), 3.69 (s, 2H), 3.50 (br d, J=11.6 Hz, 1H), 3.27-3.22 (m, 2H), 3.12-3.03 (m, 2H), 2.57 (q, J=7.1 Hz, 4H), 2.50-2.39 (m, 2H), 2.04 (s, 3H), 1.87 (br t, J=13.6 Hz, 2H), 1.10-1.05 (m, 9H); IR (KBr) 3167, 2967, 2962, 1737, 1257, 1205, 1172, 1071.

Analysis calculated for $C_{32}H_{40}N_2O_4 \cdot C_2H_4O_2$:

C, 70.81; H, 7.69; N, 4.86.

Found: C, 70.72; H, 7.64; N, 4.82.

The HCl salt of the (1S*,2S*)-title product recrystallized from ethanol/ether had: m.p. 180-184°C.

Analysis calculated for $C_{32}H_{40}N_2O_4 \cdot 2HCl \cdot 0.5\ H_2O$:

C, 64.20; H, 7.24; N, 4.61.

Found: C, 64.02; H, 7.29; N, 4.42.

By the same method the other products of the preceding Example are converted to:

(1S*,2S*)- and (1R*,2S*)-1-(4-(4-Diethylaminomethyl)-benzoyloxy)phenyl)-2-(3-(phenylthio-8-azabicyclo[3.2.1]-oct-8-yl)-1-propanol;

(1S*,2S*)- and (1R*,2S*)-2-(3-(4-Chlorophenylthio)-8-azabicyclo[3.2.1]oct-8-yl)-1-(4-(4-diethylaminomethyl)-benzoyloxy)phenyl-1-propanol;

(1S*,2S*)- and (1R*,2S*)-1-(4-(4-Diethylaminomethyl)-benzoyloxy)phenyl)-2-(2-(thienylthio)-8-azabicyclo[3.2.1]-oct-8-yl)-1-propanol;

(1S*,2S*)- and (1R*,2S*)-2-(3-Benzyl-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl)-1-(4-(4-diethylamino-ethyl)benzoyloxy)phenyl)-1-propanol; and

(1S*,2S*)- and (1R*,2S*)-2-(3-Hydroxy-3-phenyl-8-azabicyclo[3.2.1]oct-8-yl)-1-(4-(4-diethylaminoethyl)-benzoyloxy)phenyl)-1-propanol.

EXAMPLES 5-10

Substituting an equivalent amount of benzoic acid or of the appropriately substituted benzoic acid for the 4-(morpholinomethyl)benzoic acid, the method of Example 1 was used to prepare the following additional compounds:

5. 2-(4-Hydroxy-4-phenylpiperidino)-1-(4-(4-((1,1-dimethylethyl)aminomethyl)benzoyloxy)phenyl)-1-propanone; m.p. 156°C (hexane trituration, 47% yield).

6. 1-(4-(Benzoyloxy)phenyl)-2-(4-hydroxy-4-phenyl-piperidino)-1-propanone.

7. 2-(4-Hydroxy-4-phenylpiperidino)-1-(4-(4-(piperidinomethyl)benzoyloxy)phenyl)-1-propanone.

8. 2-(4-Hydroxy-4-phenylpiperidino)-1-(4-(4-(2-methylpiperidinomethyl)benzoyloxy)phenyl)-1-propanone.

9. 2-(4-Hydroxy-4-phenylpiperidino)-1-(4-(4-(di-methylaminomethyl)benzoyloxy)phenyl-1-propanone.

10. 1-(4-(3-(Di thylaminomethyl)benzoyloxy)phenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanone.

EXAMPLE 11

Racemic (1S*,2S*)-2-(4-Hydroxy-4-phenylpiperidino)-1-(4-(4-((1,1-dimethylethyl)aminomethyl)benzoyloxy)phenyl)-1-propanol

Lithium aluminum hydride (0.08 g, 2.11 mmol) was slurried in dry tetrahydrofuran (12 mL) and chilled to -78°C. The ketone product of Example 5 (0.44 g, 0.86 mmol) was added neat all at once to this cold slurry followed by continued stirring at -78°C for 1 hour. The mixture which had now become a gel was diluted with tetrahydrofuran (10 mL) and quenched with acetic acid (0.48 mL, 8.4 mmol). The solvent was removed at reduced pressure and the residue was flash chromatographed on silica gel (1 x 6 inches, packed in 30% ethyl acetate/hexane). Ethyl acetate/hexane gradient elution gave no product. Continued elution with 10% methanol/ethyl acetate yielded the product as an actate salt. This solid was suspended in ethyl acetate and vigorously shaken with saturated sodium bicarbonate. The phases were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layer was dried over calcium sulfate and concentrated. The residue was recrystallized from methanol to afford 30 mg (6.7%) of the title product as a white solid; m.p. 195-197°C; NMR ($CDCl_3$) 8.15 (d, J=8.5 Hz, 2H), 7.53 (t, J=7 Hz, 4H), 7.48-7.24 (m, 5H), 7.20 (d, J=8.5 Hz, 2H), 4.34 (d, J=9.5 Hz, 1H), 3.85 (s, 2H), 3.13 (long range coupled t, J=10.5 Hz, 1H), 2.86-2.61 (m, 4H), 2.38-2.09 (sym m, 2H), 1.88 (br d, J=13.5 Hz, 2H), 1.38 (small impurity), 1.26 (s, 1H), 0.90 (d, J=6.5 Hz, 3H). One hydroxyl proton was not observed.

Analysis calculated for $C_{32}H_{40}N_2O_4$:

C, 74.39; H, 7.80; N, 5.42.

Found: C, 73.98; H, 7.80; N, 5.18.

EXAMPLES 12-16

Using the ketone reduction procedures of the prior Examples, the ketones of Examples 6-10 were converted to the following racemic compounds:

12a. (1S*,2S*)-1-(4-(Benzoyloxy)phenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol; 38% yield; m.p. 166°C (from ethanol).

12b. (1R*,2S*)-1-(4-(Benzoyloxy)phenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol; 17% yield; m.p. 188-191°C (from ethanol).

13a. (1S*,2S*)-2-(4-Hydroxy-4-phenylpiperidino)-1-(4-(4-(piperidinomethyl)benzoyloxy)phenyl)-1-propanol; 29% yield; m.p. 175°C (dec), (from ethyl acetate).

13b. (1R*,2S*)-2-(4-Hydroxy-4-phenylpiperidino)-1-(4-(4-(piperidinomethyl)benzoyloxy)phenyl)-1-propanol; 15% yield; m.p. 167°C (dec), (from ethyl acetate).

14a. (1S*,2S*)-2-(4-Hydroxy-4-phenylpiperidino)-1-(4-(4-(2-methylpiperidinomethyl)benzoyloxy)phenyl)-1-propanol; 37% yield; m.p. 179°C (dec), (from ethyl acetate).

14b. (1R*,2S*)-2-(4-Hydroxy-4-phenylpiperidino)-1-(4-(4-(2-methylpiperidinomethyl)benzoyloxy)phenyl)-1-propanol; 16% yield; m.p. 160°C (dec), (from ethyl acetate).

15a. (1S*,2S*)-2-(4-Hydroxy-4-phenylpiperidino)-1-(4-(4-(2-dimethylaminomethyl)benzoyloxy)phenyl)-1-propanol; 7% yield; m.p. 195-198°C (dec), (from methanol).

15b. (1R*,2S*)-2-(4-Hydroxy-4-phenylpiperidino)-1-(4-(4-(2-dimethylaminomethyl)benzoyloxy)phenyl)-1-propanol; 26% yield; m.p. 162-182°C (dec), (from ethyl acetate).

16. (1S*,2S*)-1-(4-(3-(Diethylaminomethyl)benzoyloxy)phenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol; 14% yield; m.p. 119-123°C (from methylcyclohexane).

EXAMPLE 17

Racemic (1S*,2S*)-1-(4-(4-(Diethylaminomethyl)benzoyloxy)phenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol

Carbonyl diimidizole (0.25 g, 1.54 mmol) and racemic (1S*,2S*)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol hydrochloride (0.37 g, 1.52 mmol; Chenard, International Patent Application Publication No. WO 90/14088, Example 38 at page 42) in dry CH_2Cl_2 (10 ml) were stirred for 1 hour at ambient temperature. 4-(Diethylaminomethyl)benzoic acid (0.50 g, 1.53 mmol) was then added and the resulting mixture was stirred overnight. The reaction mixture was then washed with saturated $NaHCO_3$, H_2O and brine, dried with $MgSO_4$ and concentrated to give a white solid (0.41 g) which ^{1}HNMR ($CDCl_3$) showed to be a mixture of the acid, desired monoester and undesired diesterified material. Purification by silica gel flash chromatography (1 x 6 inches, ethyl acetate/hexane gradient for elution) gave 100 mg of crude title product as a colorless oil. This material was recrystallized from ethanol to yield purified title product (33 mg, 4.2%) having properties identical with those of the (1S*,2S*)-title product of Example 4.

By the same method, the enantiomeric (1S,2S)- and (1R,2R)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanols (WO 90/14088, Example 78 at page 47) are converted to the corresponding 4-(diethylaminomethyl)benzoate esters.

PREPARATION

1-(4-Hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanone

1-(4-(Triisopropylsilyloxy)phenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanone (International Application Publication Number: WO 90/14088, Example 36 at page 41; 22.0 g, 45.7 mmol) was dissolved in dry tetrahydrofuran (500 mL). Tetrabutylammonium fluoride (55 ml, 55 mmol, 1N in tetrahydrofuran) was added dropwise to the stirred solution over 3 minutes. After stirring for 1 hour, the reaction mixture was concentrated and the concentrate flash chromatographed on silica gel (3 x 6 inches). The column was gradiently eluted with ethyl acetate/hexane, then sequentially with 100% ethyl acetate, 1:9 methanol:ethyl acetate and finally with 1:5 methanol:ethyl acetate. Product-containing fractions were stripped to yield 16.7 g (100%) of title product as a light yellow solid which was triturated with hexane; m.p. 95-97°C; ^{1}H-NMR ($CDCl_3$) delta (ppm) 8.08 (d, J=8.5 Hz, 2H), 7.48 (d, J=8 Hz, 2H), 7.34 (t, J=8 Hz, 2H), 7.28-7.25 (m, 1H partially obscured by $CHCl_3$ from NMR solvent), 6.89 (d, J=8.5 Hz, 2H), 4.15 (q, J=7 Hz, 1H), 3.0-2.65 (m, 4H), 2.25-2.10 (m, 2H), 1.85-1.77 (m, 2H), 1.35 (d, J=7 Hz, 3H).

By the same method, other triisopropylsilyl protected ketones of said WO 90/14088 were converted to unprotected ketones as follows:

2-(4-Benzyl-4-hydroxypiperidino)-1-(4-hydroxyphenyl)-1-propanone;

2-(4-(4-Chlorophenyl)-4-(hydroxypiperidino)-1-(4-hydroxyphenyl)-1-propanone;

1-(4-Hydroxyphenyl)-2-(3-(phenylthio)-8-azabicyclo[3.2.1]oct-8-yl)-1-propanone;

2-(3-(4-Chlorophenylthio)-8-azabicyclo[3.2.1]oct-8-yl)-1-(4-hydroxyphenyl)-1-propanone;

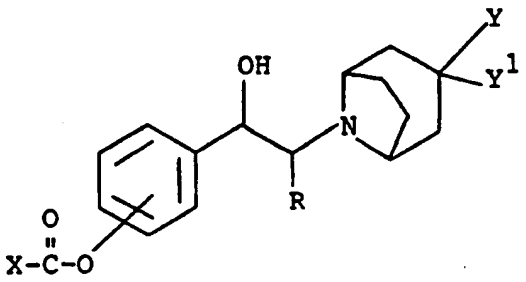
1-(4-Hydroxyphenyl)-2-(3-(2-thienylthio)-8-azabicyclo[3.2.1]oct-8-yl)-1-propanone;

2-(3-Benzyl-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl)-1-(4-hydroxyphenyl)-1-propanone; and

1-(4-Hydroxyphenyl)-2-(3-hydroxy-3-phenyl-8-azabicyclo[3.2.1]oct-8-yl)-1-propanone.

CLAIMS

1. A compound of the formula

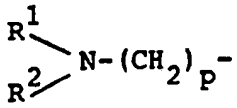


---(I)

wherein

R is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

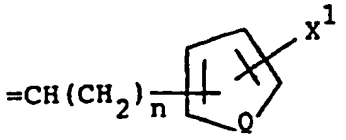
X is phenyl, benzyl, (C_1-C_3)alkoxy, phenoxy or one of said groups substituted on aromatic carbon by



p is 1 or 2;

R^1 and R^2 are taken separately and are each independently hydrogen or (C_1-C_6)alkyl, or R^1 and R^2 are taken together with the nitrogen to which they are attached to form a pyrrolidine, piperidine or morpholine ring, or one of said rings substituted by (C_1-C_3)alkyl;

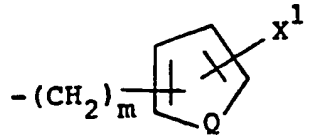
Y and Y^1 are taken together and are



; or

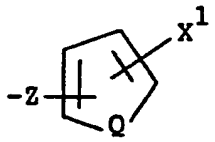
Y and Y^1 are taken separately and

Y is hydrogen or OH, and Y^1 is



; or

Y is hydrogen and Y^1 is



;

n is 0, 1, 2 or 3;

m is 0, 1, 2, 3 or 4;

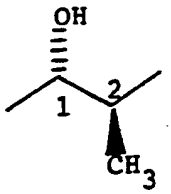
Q is S or CH=CH;

X^1 is hydrogen, (C_1-C_3)alkyl, (C_1-C_3)alkoxy or halo; and

Z is O, S, SO or SO_2; or

a pharmaceutically-acceptable acid addition salt thereof.

2. A compound of claim 1 wherein R is methyl having 1S*,2S* relative stereochemistry:



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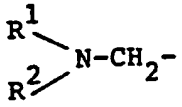
3. A compound of claim 2 wherein X is phenyl or phenyl substituted by a group



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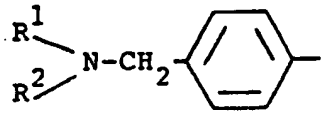
4. A compound of claim 3 wherein the group $X-\overset{O}{\overset{\|}{C}}-O-$ is substituted para to the 1-hydroxyalkyl group.

5. A compound of claim 4 wherein Y and Y^1 are taken separately.

6. A compound of claim 5 wherein X is phenyl.

7. A compound of claim 5 wherein X is



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8. A compound of claim 7 wherein R^1 and R^2 are taken separately, and R^1 and R^2 are each methyl or ethyl, or R^1 is hydrogen and R^2 is 1,1-dimethylethyl.

9. A compound of claim 8 wherein R^1 and R^2 are each ethyl.

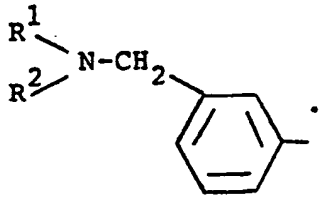
10. A compound of claim 9 wherein Y is H and Y^1 is phenylthio or 4-chlorophenylthio.

11. The compound of claim 9 wherein Y is H and Y^1 is 2-thienylthio.

12. A compound of claim 9 wherein Y is OH and Y^1 is phenyl or benzyl.

13. A compound of claim 7 wherein R^1 and R^2 are taken together with the nitrogen to which they are attached to form a morpholine, a piperidine or a 2-methylpiperidine ring.

14. A compound of claim 4 wherein X is



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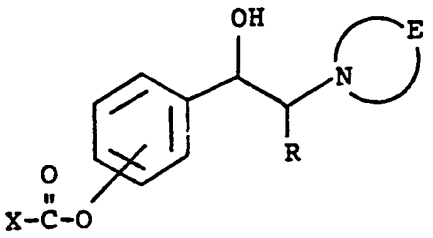
15. A compound of claim 14 wherein R^1 and R^2 are taken separately and are each ethyl.

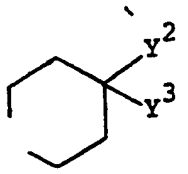
16. A compound of the formula



---(II)

wherein

E is



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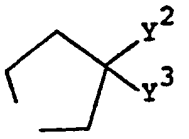
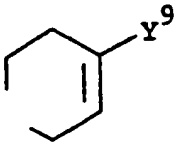


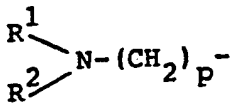
or



;

R is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

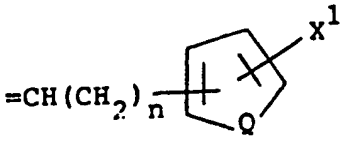
X is phenyl, benzyl, (C_1-C_3)alkoxy, phenoxy or one of said groups substituted on aromatic carbon by



p is 1 or 2;

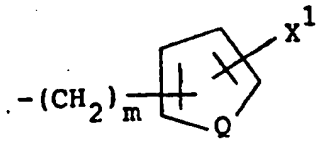
R^1 and R^2 are taken separately and are each independently hydrogen or (C_1-C_6)alkyl, or R^1 and R^2 are taken together with the nitrogen to which they are attached to form a pyrrolidine, piperidine or morpholine ring, or one of said rings substituted by (C_1-C_3)alkyl;

Y^2 and Y^3 are taken together and are



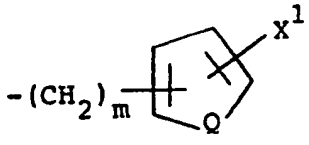
; or

Y^2 and Y^3 are taken separately, and Y^2 is OH and Y^3 is



;

Y^9 is



;

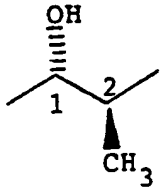
n is 0, 1, 2 or 3;

m is 0, 1, 2, 3 or 4;

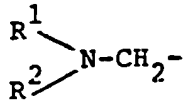
Q is S or CH=CH; and

X^1 is hydrogen, (C_1-C_3)alkyl, (C_1-C_3)alkoxy or halo; or a pharmaceutically-acceptable acid addition salt thereof.

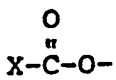
17. A compound of claim 16 wherein R is methyl having 1S*,2S* relative stereochemistry:



18. A compound of claim 17 wherein X is phenyl or phenyl substituted by a group

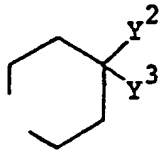


19. A compound of claim 18 wherein the group



is substituted para to the 1-hydroxyalkyl group.

20. A compound of claim 19 wherein E is

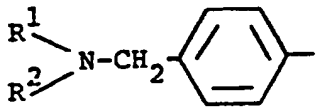


and Y^2 and Y^3 are taken separately.

21. A compound of claim 20 wherein X is phenyl.

22. The compound of claim 21 wherein Y^2 is OH and Y^3 is phenyl.

23. A compound of claim 20 wherein X is



24. A compound of claim 23 wherein R^1 and R^2 are taken separately, and R^1 and R^7 are each methyl or ethyl, or R^1 is hydrogen and R^2 is 1,1-dimethylethyl.

25. The compound of claim 24 wherein R^1 and R^2 are each methyl, Y^2 is OH and Y^3 is phenyl.

26. The compound of claim 24 wherein R^1 and R^2 are each ethyl, Y^2 is OH and Y^3 is phenyl.

27. The compound of claim 24 wherein R^1 is hydrogen and R^2 is 1,1-dimethylethyl, Y^2 is OH and Y^3 is phenyl.

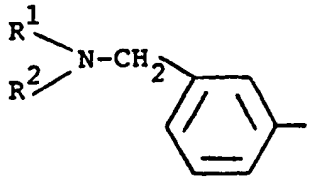
28. A compound of claim 23 wherein R^1 and R^2 are taken together with the nitrogen to which they are attached to form a morpholine, a piperidine or a 2-methylpiperidine ring.

29. The compound of claim 28 wherein R^1 and R^2 are taken together with the nitrogen to which they are attached to form a morpholine ring, Y^2 is OH and Y^3 is phenyl.

30. The compound of claim 28 wherein R^1 and R^2 are taken together with the nitrogen to which they are attached to form a piperidine ring, Y^2 is OH and Y^3 is phenyl.

31. The compound of claim 28 wherein R^1 and R^2 are taken together with the nitrogen to which they are attached to form a 2-methylpiperidine ring, Y^2 is OH and Y^3 is phenyl.

32. A compound of claim 20 wherein X is



33. The compound of claim 32 wherein R^1 and R^2 are taken separately and are each ethyl, Y^2 is OH and Y^3 is phenyl.

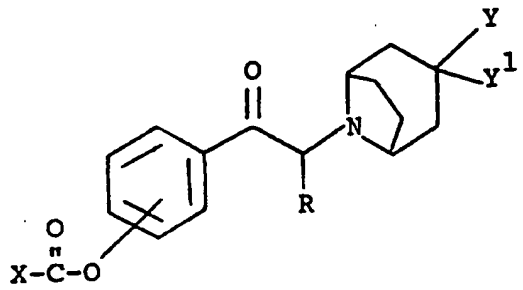
34. A pharmaceutical composition comprising a neuroprotective amount of a compound of claim 1 and a pharmaceutically-acceptable carrier.

35. A pharmaceutical composition comprising a neuroprotective amount of a compound of claim 16 and a pharmaceutically-acceptable carrier.

36. A method of treating stroke, traumatic head injury or a CNS degenerative disease in man which comprises treatment with a neuroprotective amount of a compound of claim 1.

37. A method of treating stroke, traumatic head injury or a CNS degenerative disease in man which comprises treatment with a neuroprotective amount of a compound of claim 16.

38. A compound of the formula

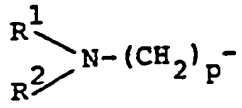


---(III)

wherein

R is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

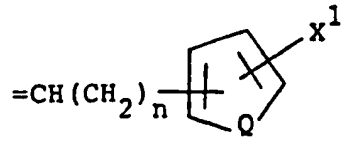
X is phenyl, benzyl, (C_1-C_3)alkoxy, phenoxy or one of said groups substituted on aromatic carbon by



p is 1 or 2;

R^1 and R^2 are taken separately and are each independently hydrogen or (C_1-C_6)alkyl, or R^1 and R^2 are taken together with the nitrogen to which they are attached to form a pyrrolidine, piperidine or morpholine ring, or one of said rings substituted by (C_1-C_3)alkyl;

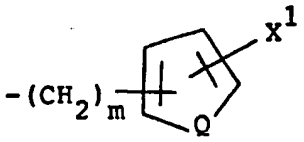
Y and Y^1 are taken together and are



; or

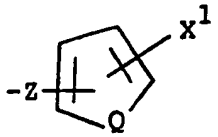
Y and Y^1 are taken separately and

Y is hydrogen or OH, and Y^1 is



; or

Y is hydrogen and Y^1 is



;

n is 0, 1, 2 or 3;

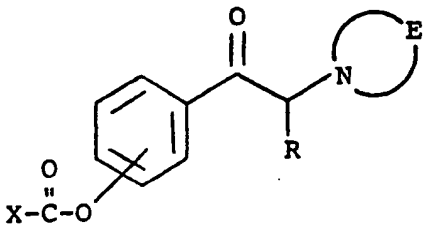
m is 0, 1, 2, 3 or 4;

Q is S or CH=CH;

X^1 is hydrogen, (C_1-C_3)alkyl, (C_1-C_3)alkoxy or halo; and

Z is O, S, SO or SO_2.

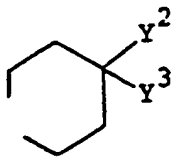
39. A compound of the formula

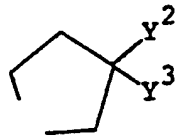


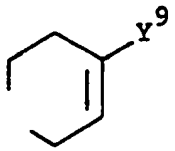
---(IV)

wherein

E is



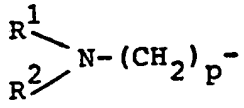
,


or


;

R is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

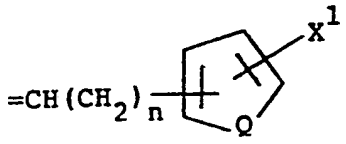
X is phenyl, benzyl, (C_1-C_3)alkoxy, phenoxy or one of said groups substituted on aromatic carbon by



p is 1 or 2;

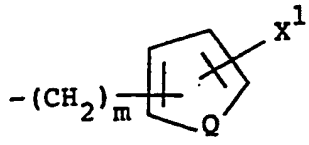
R^1 and R^2 are taken separately and are each independently hydrogen or (C_1-C_6)alkyl, or R^1 and R^2 are taken together with the nitrogen to which they are attached to form a pyrrolidine, piperidine or morpholine ring, or one of said rings substituted by (C_1-C_3)alkyl;

Y^2 and Y^3 are taken together and are



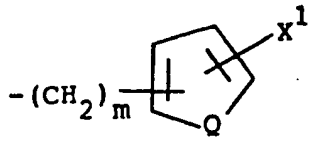
; or

Y^2 and Y^3 are taken separately, and Y^2 is OH and Y^3 is



;

Y^9 is



;

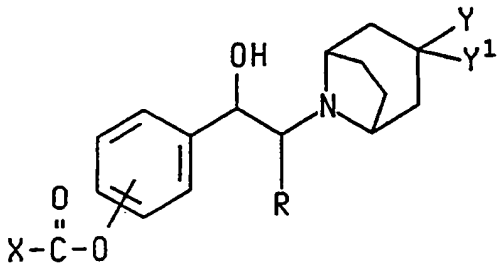
n is 0, 1, 2 or 3;

m is 0, 1, 2, 3 or 4;

Q is S or CH=CH; and

X^1 is hydrogen, (C_1-C_3)alkyl, (C_1-C_3)alkoxy or halo.

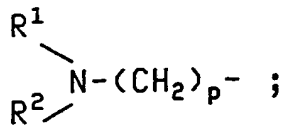
40. A process for preparing a compound of the formula



wherein

R is H, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

X is phenyl, benzyl, $(C_1\text{-}C_3)$alkoxy, phenoxy or one of said groups substituted on aromatic carbon by

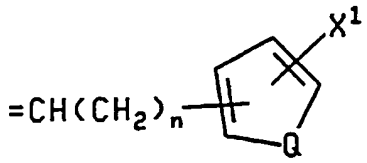


;

p is 1 or 2;

R^1 and R^2 are taken separately and are each independently hydrogen or $(C_1\text{-}C_6)$alkyl, or R^1 and R^2 are taken together with the nitrogen to which they are attached to form a pyrrolidine, piperidine or morpholine ring, or one of said rings substituted by (C_1C_3)alkyl;

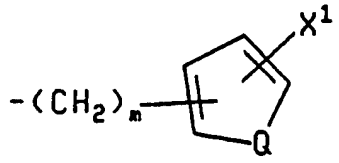
Y and Y^1 are taken together and are



; or

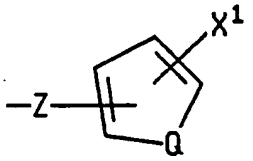
Y and Y^1 are taken separately and

Y is hydrogen or OH, and Y^1 is



; or

Y is hydrogen and Y^1 is



;

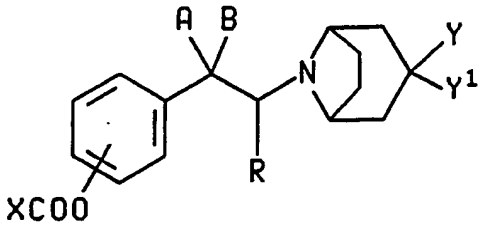
n is 0, 1, 2 or 3;

m is 0, 1, 2, 3 or 4;

Q is S or CH=CH;

X^1 is hydrogen, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy or halo; and

Z is O, S, SO or SO_2 comprising reacting a compound of the formula

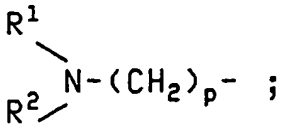


wherein

R is H, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

A and B are taken together and are oxygen (forming a carbonyl with the carbon atom);

X is phenyl, benzyl, $(C_1\text{-}C_3)$alkoxy, phenoxy or one of said groups substituted on aromatic carbon by



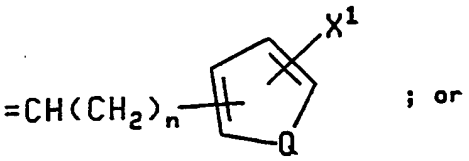
;

p is 1 or 2;

R^1 and R^2 are taken separately and are each ind p ndently hydrogen or

$(C_1$-$C_6)$alkyl, or R^1 and R^2 are taken together with the nitrogen to which th y ar attached to form a pyrrolidine, piperidine or morpholine ring, or one of said rings substituted by (C_1C_3)alkyl;

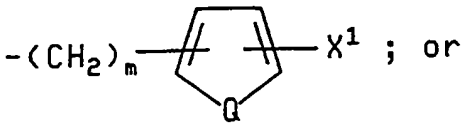
Y and Y^1 are taken together and are



; or

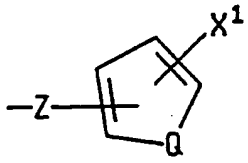
Y and Y^1 are taken separately and

Y is hydrogen or -OH, and Y^1 is



; or

Y is hydrogen and Y^1 is



;

n is 0, 1, 2 or 3;

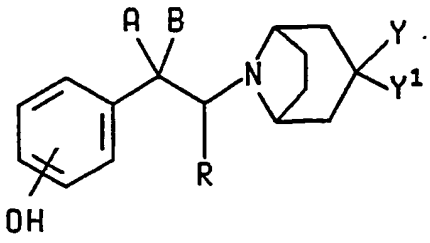
m is 0, 1, 2, 3 or 4;

Q^1 is S or -CH=CH-;

X^1 is hydrogen, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$alkoxy or halo; and

Z is O, S, SO or SO_2 with an excess of a hydride reducing agent in a reaction inert solvent at about -78°C to about 0°C for about 15 minutes to about 24 hours.

41. The process according to claim 1 comprising the additional prior step of reacting a compound of the formula

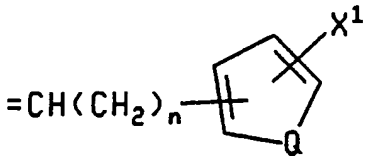


wherein

R is H, (C_1-C_6) alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

A and B are taken together and are oxygen (forming a carbonyl with the carbon atom);

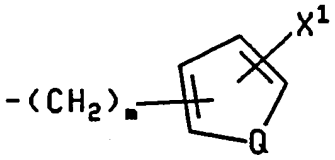
Y and Y^1 taken together and are



; or

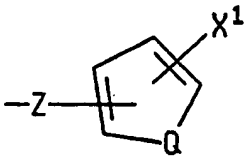
Y and Y^1 are taken separately and

Y is hydrogen or OH, and Y^1 is



; or

Y is hydrogen and Y^1 is



;

n is 0, 1, 2 or 3;

m is 0, 1, 2, 3 or 4;

Q is S or CH=CH;

X^1 is hydrogen, (C_1-C_3)alkyl, (C_1-C_3)alkoxy or halo; and

Z is O, S, SO or SO_2 with an organic acid of the formula X-COOH, wherein X is phenyl, benzyl, (C_1-C_3)alkoxy, phenoxy or one of said groups substituted on aromatic carbon by

wherein R^1 and R^2 are

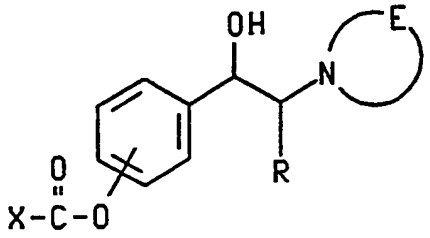
taken separately and are each independently hydrogen or (C_1-C_6)alkyl, or R^1 and R^2 are taken together with nitrogen to which they are attached to form a pyrrolidine, piperidine or morpholine ring, or one of said rings substituted by (C_1-C_3)alkyl); and p is 1 or 2 in the presence of an esterifying agent in a reaction inert solvent at a temperature of about 0°C to about 50°C for about 15 minutes to about 24 hours.

42. The process according to claim 41 wherein the esterifying agent is a peptide coupling reagent.

43. The process according to claim 42 wherein the peptide coupling reagent is 1-ethyl-3-(3-dimethyl-aminopropyl)-carbodiimide and additionally comprising adding triethylamine.

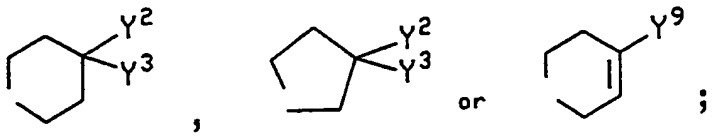
44. The process according to claim 43 wherein the hydride reducing agent is sodium borohydride.

45. A process for preparing a compound of the formula



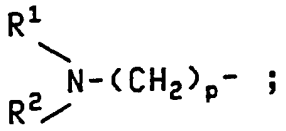
wherein

E is



R is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

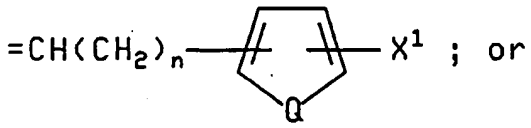
X is phenyl, benzyl, (C_1-C_3)alkoxy, phenoxy or one of said groups substituted on aromatic carbon by



p is 1 or 2;

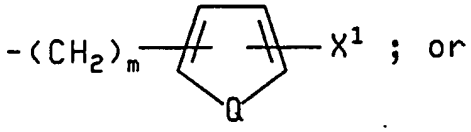
R^1 and R^2 are taken separately and are each ind pendently hydrogen or $(C_1\text{-}C_6)$alkyl, or R^1 and R^2 are taken together with the nitrogen to which they are attached to form a pyrrolidine, piperidine or morpholine ring, or one of said rings substituted by $(C_1\text{-}C_3)$alkyl;

Y^2 and Y^3 are taken together and are



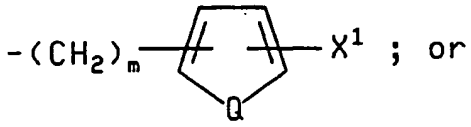
; or

Y^2 and Y^3 are taken separately, and Y^2 is OH and Y^3 is



; or

Y^3 is



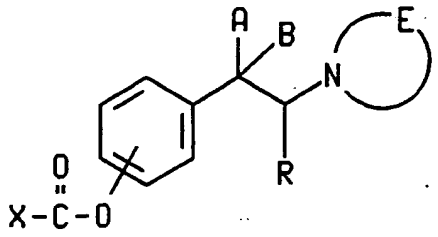
; or

n is 0, 1, 2 or 3;

m is 0, 1, 2, 3 or 4;

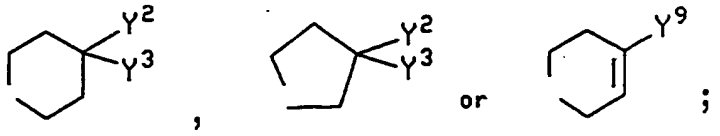
Q is S or CH=CH; and

X^1 is hydrogen, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy or halo comprising reacting a compound of the formula



wherein

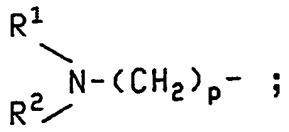
E is



R is H, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

A and B are taken together and are oxygen (forming a carbonyl with the oxygen atom);

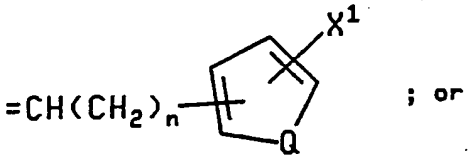
X is phenyl, benzyl $(C_1\text{-}C_3)$alkoxy, phenoxy or one of said groups substituted on aromatic carbon by



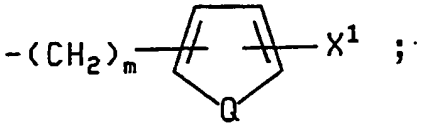
p is 1 or 2;

R^1 and R^2 are taken separately and are each independently hydrogen or $(C_1\text{-}C_6)$alkyl, or R^1 and R^2 are taken together with the nitrogen to which they are attached to form a pyrrolidine, piperidine or morpholine ring, or one of said rings substituted by $(C_1\text{-}C_3)$alkyl;

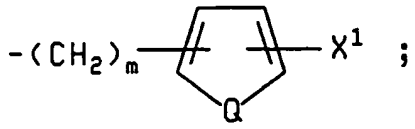
Y^2 and Y^3 are taken together and are



Y^2 and Y^3 are taken separately, and Y^2 is OH and Y^3 is



Y^9 is



;

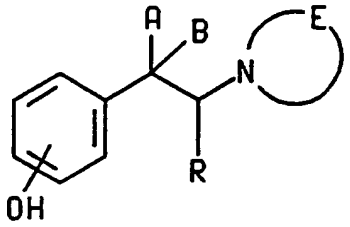
n is 0, 1, 2 or 3;

m is 0, 1, 2, 3 or 4;

Q is S or CH=CH; and

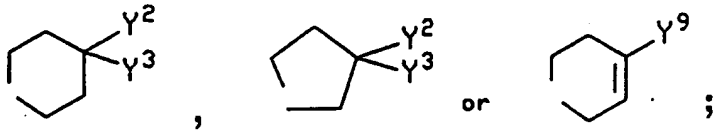
X^1 is hydrogen, (C_1-C_3)alkyl, (C_1-C_3)alkoxy or halo with an excess of a hydride reducing agent in a reaction inert solvent at about -78°C to about 0°C for about 15 minutes to about 24 hours.

46. The process according to claim 45 comprising the additional prior step of reacting a compound of the formula



wherein

E is

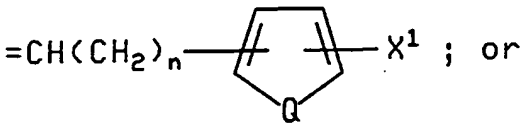


;

R is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

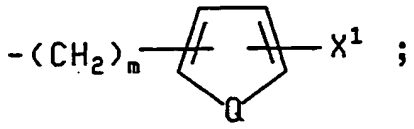
A and B are taken together and are oxygen (forming a carbonyl with the carbon atom);

Y^2 and Y^3 are taken together and ar



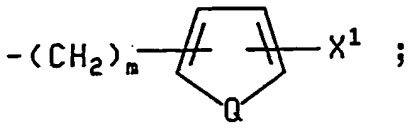
5

Y^2 and Y^3 are taken separately, and Y^2 is OH and Y^3 is



10

Y^9 is



15

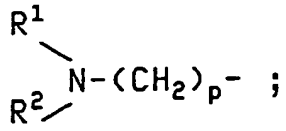
n is 0, 1, 2 or 3;

20 m is 0, 1, 2, 3 or 4;

Q is S or CH=CH; and

X^1 is hydrogen, (C_1-C_3)alkyl, (C_1-C_3)alkoxy or halo with an organic acid of the formula X-COOH, wherein X is phenyl, benzyl, (C_1-C_3)alkoxy, phenoxy or one of said groups substituted on aromatic carbon by

25



wherein R^1 and R^2 are taken separately and are each independently hydrogen or

30 (C_1-C_6)alkyl, or R^1 and R^2 are taken together with nitrogen to which they are attached to form a pyrrolidin , piperidin or morpholine ring, or one of said rings substituted by (C_1-C_3)alkyl; and p is 1 or 2 in the presence of an esterifying agent in a reaction inert solvent at a temperature of about 0°C to ab ut 50°C for about 15 minutes to about 24 hours.

47. The process according to claim 46 wherein the esterifying agent is a peptide coupling reagent.

48. The process according to claim 47 wherein the peptide coupling reagent is 1-ethyl-3-(3-dimethyl-aminopropyl)-carbodiimide and additionally comprising adding triethylamine.

49. The process according to claim 48 wherein the hydride reducing agent is sodium borohydride.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/02131

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D451/02; A61K31/33; C07D451/06; C07D207/02
C07D211/04; C07D211/68; C07D409/02

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	WO,A,9 014 088 (PFIZER) 29 November 1990 cited by the Applicant see the whole document ---	1-49
X	WO,A,9 014 087 (PFIZER) 29 November 1990 cited by Applicant see the whole document ---	1-49
P,Y	EP,A,0 441 506 (PFIZER) 14 August 1991 see the whole document ---	1-49
P,Y	WO,A,9 117 156 (PFIZER) 14 November 1991 see the whole document ---	1-49

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
22 JULY 1992	19. 08. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT FFICE	GETTINS M.P.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	JOURNAL OF MEDICINAL CHEMISTRY vol. 32, no. 12, December 1989, USA pages 2503 - 2507; BUNDGAARD ET AL: 'A novel solution-stable,water-prodrug Type' cited by applicant ---	1-49

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9202131 SA 59848

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 22/07/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9014088	29-11-90	WO-A- 9014087	29-11-90
		CA-A- 2016860	17-11-90
		EP-A- 0398578	22-11-90
WO-A-9014087	29-11-90	CA-A- 2016860	17-11-90
		EP-A- 0398578	22-11-90
		WO-A- 9014088	29-11-90
EP-A-0441506	14-08-91	WO-A- 9112005	22-08-91
		DE-U- 9101346	06-06-91
WO-A-9117156	14-11-91	AU-A- 7456591	27-11-91
		CN-A- 1056497	27-11-91